Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 1s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Effect of Omega-3 Fatty Acids on the Lipid Profile in Rats induced-acute cardiotoxicity by doxorubicin

Prof. Dr. Suhad Faisal Hatem Al-Mugdadi[1], Lec. Ishraq Hasan Elewi1, Lec.Zainab Farooq Shafeeq[1], Lec.Maha Mohamed Abd Ali[2], Saja Qais Hammadi[1], Mariem Salam Abd-Alraheem[1]

[1]Department of Clinical Laboratories Sciences, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.

[2]Al-Hadi University, Baghdad, Iraq.

[*]**Corresponding author:**

Email ID: suhadhatim@uomustansiriyah.edu.iq / orcid.org- 0000-0002-7164-70

.Cite this paper as: Prof. Dr. Suhad Faisal Hatem Al-Mugdadi, Lec. Ishraq Hasan Elewi, Lec.Zainab Farooq Shafeeq, Lec.Maha Mohamed Abd Ali, Saja Qais Hammadi, Mariem Salam Abd-Alraheem, (2025) Effect of Omega-3 Fatty Acids on the Lipid Profile in Rats induced-acute cardiotoxicity by doxorubicin. *Journal of Neonatal Surgery*, 14 (1s), 1227-1234.

ABSTRACT

Doxorubicin is a medication used to treat various cancers .One of the side effects of doxorubicin is cardio toxicity. Some studies have shown that omega 3 has a protective effect against doxorubicin cardio-toxicity. Also, many studies suggested there is effect of Omega-3 supplement on lipids profile. Therefore, This study aimed to evaluate the lipids profile after receiving Omega-3 in rats induced-acute cardiotoxicity by doxorubicin. The rats were divided into five groups: the first group was given normal saline, the second group was given doxorubicin, the third group was given 100 mg of OMG, the fourth group was given 200 mg of OMG, and the fifth group was given 400 mg of Omega-3. After 4 weeks, 20mg doxorubicin was given for all groups except normal saline group. Serum obtained after 48 h. lipid profile was measured according to manufacturer of company using spectrophotometer. Regarding present data, mean level of Cholesterol, triglyceride, LDL and VLDL were reduced In omg3 groups (100mg,200mg,400mg) significantly. While HDL was increased. ***Conclusion****:* The lipids profile has been better (low levels) when use Omega-3in rats induced- acute cardiotoxicity by doxorubicin. Thus, Omega-3 may consider as protective supplement in heart toxicity**.**

Keywords: *Doxorubicin , heart toxicity .lipids, Omega-3*

1. INTRODUCTION

Doxorubicin (DOX) is a necessary medication in the treatment regimen against cancers , but long-term toxicity is the primary worry for preserving the standard of living for patients .Cardiotoxicity is one of the side effects that can affect a patient's prognosis when using the medication. cardiomyocytes is caused by the chemotherapeutic agent's lack of selectivity towards cancer cells[(1,2)]

Doxorubicin causes a considerable rise in LDL, VLDL, and triglyceride levels. Free radical production, iron-dependent oxidative damage to biological macromolecules, and membrane lipid peroxidation may be the main processes by which DOX-induced injury is mediated. When rats were given DOX, they developed free radicals and had an antioxidant insufficiency. According to one research, the doxorubicin-treated group showed higher levels of malondialdehyde while superoxide dismutase and catalase activity declined. They reported that the rats treated with DOX had considerably higher blood concentrations of triglycerides and total cholesterol. Because DOX causes membrane lipids to peroxide, which causes the release of cholesterol and protein into the bloodstream from the cytosol, it has the power to fundamentally alter the chemical structure, and function of biological membranes, primarily at the mitochondrial level [(3,4)] .

A risk factor for cardiovascular disease (CVD) is elevated triglycerides.[(5)] Omega 3 PUFAs have been linked to improvement in lipid profile[(6)] .When taken at the right times and in the right amounts, long chain fatty acids, also referred to as omega 3, have many positive effects on the body. Recent research indicates that omega 3 can improve the antitumor efficaciousness of adjuvant chemotherapy drugs, including gemcitabine, carboplatin, and anthracyclines [(7)].Despite the adverse effects of DOX and its significance in the treatment of cancer, policies that enable its safe use are of vital importance. According to preclinical research conducted on rats ,natural dietary upplements, such as omega 3 containing minerals, vitamins, and polyunsaturated fatty acids, may be able to mitigate or neutralize these negative effects [(8)] . Other authors have demonstrated that the advantages of omega-3 EFAs on coronary mortality are attributable to their effects on cardiac arrhythmia (9), platelet

aggregation, and hemostatic factors. [10,11,12] and vascular reactivity [11]. In addition to how they affect lipid metabolism[13,14]. This study aimed to evaluate the cardioprotective effects of omega 3 at different doses by measuring the lipid levels using spectrophotometer on rats suffering from acute cardiotoxicity by induction with DOX .

2. MATERIALS AND METHODS

The ethics committee of Mustansiriyah University's College of Pharmacy in Baghdad, Iraq, approved this study. Baghdad, Iraq.

Source of animals

Female Wistar rats measuring 180-200 g and 16 weeks old were utilized in this investigation. The animals were obtained from the Animal Care and Research Unit at Mustansiriyah University's College of Pharmacy in Baghdad. The animals were housed under standardized circumstances.

Experimental groupings

The Wistar rats were randomly allocated into five groups, each with 4-6 individuals, as follows: Group 1 received just distilled water; Group 2 received a single dosage of DOX (20 mg/kg); and Groups 3-5 received varying doses of OMG-3 (100,200,400 mg/kg/day) orally for four weeks by gavage. To produce acute cardiotoxicity, rats in groups 3-5 were given a single intraperitoneal injection of DOX (20 mg/kg) 24 hours after the final doses of OMG-3. [15].

Collection of blood samples

After two days from DOX administration, 200 µl of blood was obtained from each rat by heart puncture then the serum was separated . Lipid analysis was done on a fully automated analyzer based on Enzymatic colorimetric test (Spectrophotometer) .

Lipid profile

The procdure of Cholesterol ,Triglycerides, HDL-Cholesterol, LDL and VLDL was done regarding to the manufacture procedure ,LINEAR CHEMICALS S.L. Joaquim Costa 18 2a planta. 08390 Montgat, Barcelona, SPAIN [16].

Statistical Analysis:

The Statistical Analysis System- SAS (2018) application was used to determine the influence of different variables on research parameters. In this study, the least significant difference (LSD) test (Analysis of Variation-ANOVA) was utilized to significantly compare means. Result considered significant in p-value 0.05 and less.

3. RESULTS

Cholestrol Level Regarding to the Table (1) and Figure (1) , the groups received Omega-3 (100,200 and 400mg) were low mean level of cholesterol compare to groups of doxorubicin alone with significant difference ** (P≤0.01).

Table (1): Mean of Cholesterol level in all groups in this study

Groups	Mean ± SE of Cholesterol (mg/dl)
Group 1 (Control)	190.0445 ±12.38 b
Group 2 (DOX)	262.159 ±16.73 a
Group 3 (100mg)	207.527 ±12.66 b
Group 4 (200 mg)	194.693 ±9.85 b
Group 5 (400mg)	192.274 ±11.35 b
LSD value	32.471 **
P-value	0.0083
Means having with the different letters in column differed significantly. ** (P≤0.01).	

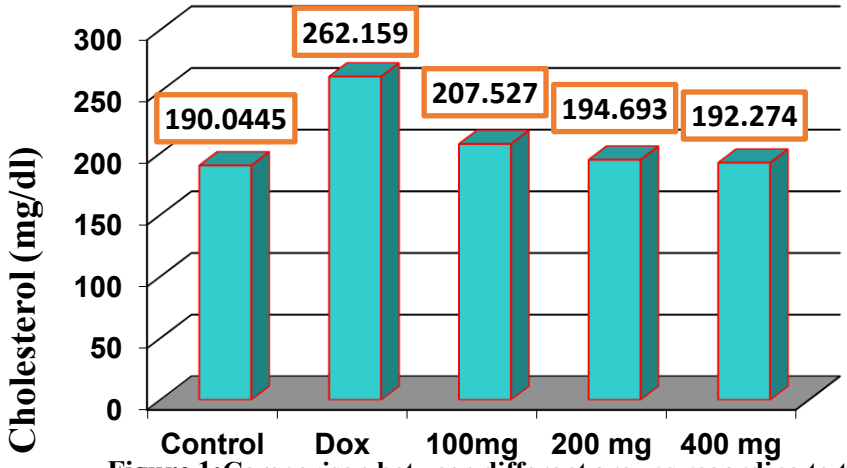

Figure 1:Comparison between different groups regarding to the Cholesterol level

Triglycerides MR level The groups of Omeg-3 (100,200 and 400mg) were lower mean of the triglyceride level than the groups of doxorubicin alone and control with significant difference

Table (2): Mean of Triglycerides level in all study groups

Groups	Mean ± SE of Triglyceride (mg/dl)
Group 1(Control)	254.6 ±11.94 ab
Group 2 (Dox)	273.2 ±14.58 a
Group 3(100mg)	249.59 ±11.02 ab
Group 4(200 mg)	228.98 ±8.47 b
Group 5 (400mg)	217.43 ±8.26 b
LSD value	41.229 *
P-value	0.0387
Means having with the different letters in column differed significantly. * (P≤0.05).	

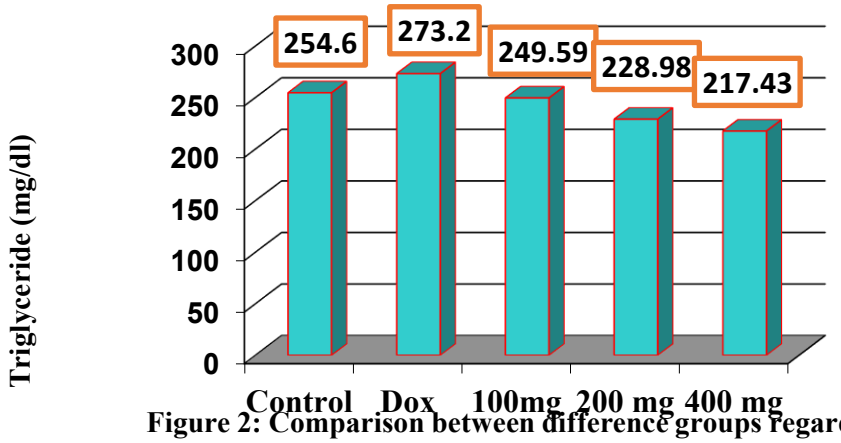

Figure 2: Comparison between difference groups regarding to the Triglyceride level

* (P≤0.05) ,as illustrated in Table (2) and Figure (2).

HDL-Cholestrol level The groups of Omeg-3 (100,200 and 400mg) were higher mean of HDL level than the groups of doxorubicin alone with significant difference** (P≤0.01) ,as illustrated in Table (3) and Figure(3).

Table (3): Mean of HDL level in all study groups

Groups	Mean ± SE of HDL (mg/dl)
Group 1(Control)	38.78 ±2.16 ab
Group 2 (Dox)	22.15 ±1.53 d
Group 3 (100mg)	29.72 ±2.08 cd
Group 4 (200 mg)	34.79 ±2.91 bc
Group 5 (400mg)	44.02 ±3.05 a
LSD value	8.174 **
P-value	0.0026
Means having with the different letters in column differed significantly. ** (P≤0.01).	

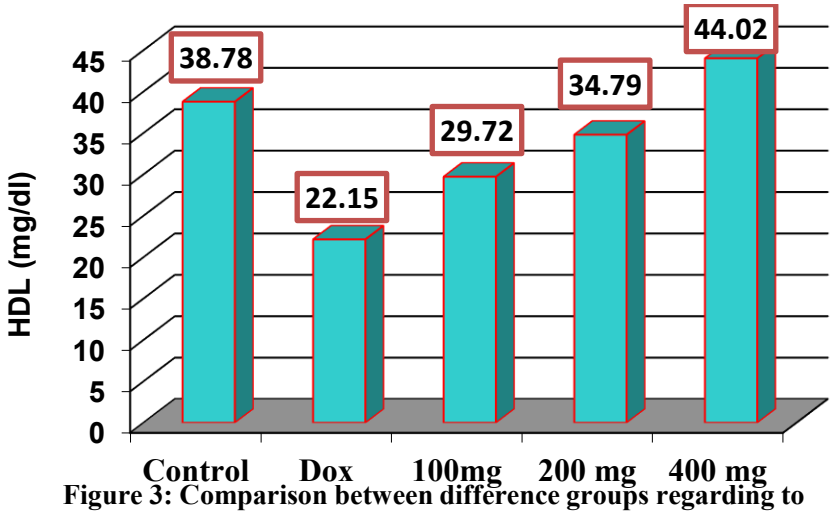

Figure 3: Comparison between difference groups regarding to the HDL level

LDL-Cholestrol Regarding to the Table (4) and Figure(4) , the groups received Omega-3 (100,200 and 400mg) were low mean of LDL level compare to group of doxorubicin alone with significant difference ** (P≤0.01).

Table (4): Mean of LDL level in all study groups

Groups	Mean ± SE of LDL (mg/dl)
Group 1 (Control)	100.33 ±5.03 b
Group 2 (Dox)	185.36 ±11.37 a
Group 3 (100mg)	127.83 ±7.64 b
Group 4 (200 mg)	116.51 ±6.33 b
Group 5 (400mg)	102.45 ±5.18 b

LSD value	29.574 **
P-value	0.0061
Means having with the different letters in same column differed significantly ** (P ≤0.01).	

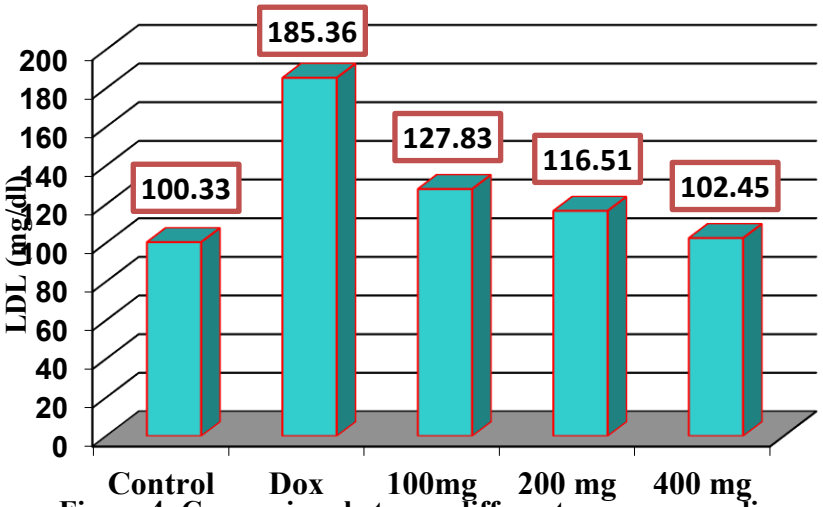

Figure 4: Comparison between different groups regarding to the LDL level

VLDL-Cholestrol Regarding to the Table (5) and Figure(5), the groups received Omega-3 (100,200 and 400mg) were low mean of VLDL level compare to group of doxorubicin alone and control with significant difference * (P≤0.05).

Table (5): Mean of VLDL level in all study groups

Groups	Mean ± SE of VLDL (mg/dl)
Group 1 (Control)	50.92 ±2.96 ab
Group 2 (Dox)	54.64 ±3.05 a
Group 3 (100mg)	49.69 ±2.47 abc
Group 4 (200 mg)	43.48 ±2.83 c
Group 5 (400mg)	45.79 ±2.62 bc
LSD value	7.241 *
P-value	0.0355
Means having with the different letters in same column differed significantly * (P≤0.05).	

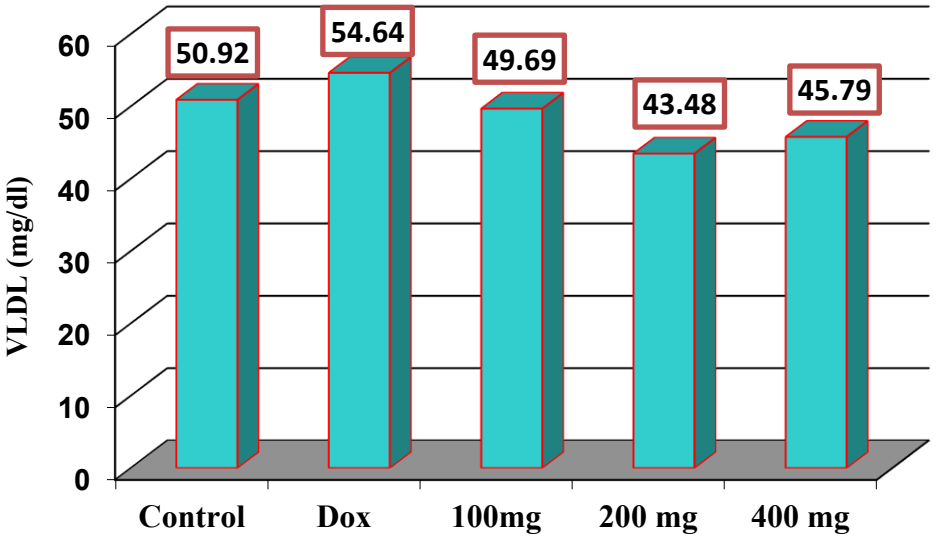

Figure 5: Comparison between difference groups regarding to the VLDL level

4. DISCUSSION

In this study, we employed the rat model to assess the effects of low-dose omega-3 fatty acid supplementation. For the majority of the measured indices, there were significant changes between the experimental and control groups. The results of this study showed that, when compared to DOX alone and control groups, omega-3 polyunsaturated fatty acids are statistically substantially related with lower levels of triglycerides, cholesterol, LDL, and VLDL, while increasing levels of HDL. According to one study, HMG-CoA reductase inhibition may be the cause of the drop in blood cholesterol. This enzyme reduces the production of cholesterol by catalyzing the conversion of HMG-CoA to mevalonate in [17] .

The magnitude of blood lipids is critical in determining if abnormal lipid levels raise CVD risk [18]. The particle size and density of low-density lipoproteins fluctuate, which is associated with their capacity to produce vascular oxidative damage and blood vessel plaque development. Lipid subtype studies has demonstrated that the predominance of small LDL is a much more significant cardiovascular risk factor than other subtypes. While higher HDLs are typically regarded to be protective against the development of CVD due to their size, larger LDL subfractions are less commonly associated withCVD.[19]

Omega-3 fatty acids have been shown to decrease triglyceride levels via reducing VLDL synthesis in the liver. Omega-3 fatty acids inhibited hepatic lipogenesis and lowered circulating triglycerides. The lower hepatic cholesterol content was compensated for by greater cholesterol release into bile, leading to a depletion of the intrahepatic pool of cholesterol. [20,21] . However, little is known about the mechanism driving the rise in HDL-c levels seen with omega-3 treatment. It might be due to a decrease in the creation of VLDL cholesterol and an increase in its elimination, or it could be the result of both processes working together in tandem. In addition, there is evidence linking the decrease in cholesteryl ester transfer protein activity to increases in HDL-c brought on by omega-3 fatty acid supplements. As is the case with statin medication, the reduction in very low-density lipoprotein and LDL particle levels may be the cause of this decline in transfer protein function. [22].

As we know, Triglyceride, LDL, and VLDL levels were all markedly elevated by DOX; this might be attributed to the generation of free radicals and an antioxidant deficiency. Because of the peroxidation of membrane lipids, which causes the release of protein and cholesterol from the cytosol into the circulation, DOX has the capacity to alter the chemical composition, structure, and function of biological membranes, primarily at the mitochondria.[3,4] HDL is known as the "good" cholesterol because it forages cholesterol from tissues and transports it to the liver for breakdown [23]. This may be the reason why HDL and its subfractions are recognized as protective factors against coronary heart disease[24,25].

It is thought that the omega-3 EFAs reduce cholesterol by preventing the liver from synthesizing vLDL. As a result, the vLDL and LDL particles become smaller and less dense, which lowers the lipid profile that causes plaque [26] .

Study limitations A limitation of this study is that Serum lipid levels are influenced by a wide range of variables, including lifestyle and nutrition, which can be challenging to regulate and balance.

Conclusion The lipids profile has been better (low levels) when use Omega-3 in rats induced- acute cardiotoxicity by doxorubicin ,thus Omega-3 may consider as protective supplement in coronary vascular diseases.

Acknowledgement The authors gratefully thank Mustansiriyah University. (www.uomustansiriyah.edu.iq) for supporting and providing the practical platform to precede this work.

REFERENCES

[1] Schilsky, Richard. (2010). Personalized medicine in oncology: The future is now. Nature reviews. Drug discovery. 9. 363-6. 10.1038/nrd3181. .

[2] Luu AZ, Chowdhury B, Al-Omran M, Teoh H, Hess DA, Verma S. Role of Endothelium in Doxorubicin-Induced Cardiomyopathy. JACC Basic Transl Sci. 2018;3(6):861-870.

[3] Malabade, RH, Rasal, VPand Ismail. Interaction of Mandarin Oil with Nicorandil in Doxorubicin Induced Myocardial Infarction. IOSR Journal of Pharmacy and Biological Sciences. 2014; 9(1): 95-98.

[4] Chen, Y, Jungsuwadee, P, Vore, M,Butterfieldand, DAand StClair, DK. Collateral damage in cancer chemotherapy: oxidative stress in non-targeted tissues. Mol. Interv, 2007;7: 147-156.

[5] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama. 2002 Jan 16;287(3):356-9.

[6] Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. circulation. 2002 Nov 19;106(21):2747-57.

[7] Theinel MH, Nucci MP, Alves AH, Dias OFM, Mamani JB, Garrigós MM, Oliveira FA, Rego GNA, Valle NME, Cianciarullo G, Gamarra LF. The Effects of Omega-3 Polyunsaturated Fatty Acids on Breast Cancer as a Preventive Measure or as an Adjunct to Conventional Treatments. Nutrients. 2023 Mar 7;15(6):1310. doi: 10.3390/nu15061310. PMID: 36986040; PMCID: PMC10052714.

[8] Varela-López A, Battino M, Navarro-Hortal MD, Giampieri F, Forbes-Hernández TY, Romero-Márquez JM, Collado R, Quiles JL. An update on the mechanisms related to cell death and toxicity of doxorubicin and the protective role of nutrients. Food and Chemical Toxicology. 2019 Dec 1;134:110834.

9- Reiffel WS, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. Am J Cardiol. 2006;98(suppl):50i-60i.

[9] Kris-Etherton PM, Harris WS, Appel LJ.American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002;106:2747-2757.

[10] Marchioli R. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet. 1999;354:447-455.

[11] Stone NJ. Fish consumption, fish oil, lipids, and coronary heart disease. Circulation. 1996;94:2337-2340.

[12] Luo J, Rizkalla SW, Vidal H, et al. Moderate intake of n-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type 2 diabetic men. Results of a controlled study. Diabetes Care. 1998;21:717-724.

[13] Minihane AM, Khan S, Leigh-Firbank EC, et al. ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype. Arterioscler Thromb Vasc Biol. 2000;20:1990-1997

[14] Haneen K. Al-hassani1, Yassir A. Hummadi1, Suhad Faisal Hatem Al-M. Protective Effect of Omega-3 and the Potential of Toll-like Receptor Gene Expression in Rats with Doxorubicin-induced Cardiac Toxicity. Trop J Nat Prod Res 2023; 7(2):2358-2361.

[15] LINEAR CHEMICALS, S.L.U. Joaquim Costa 18 2a planta. 08390 Montgat (Barcelona)

[16] SPAIN elf.(+34) 934 694 990; E-mail: info@linear.es ; website: www.linear.es NIF-VAT:B60485687.

[17] Kobatake, Yoshiki, et al. “Differential effects of dietary eicosa- pentaenoic and docosahexaenoic fatty acids on lowering of tri-glyceride and cholesterol levels in the serum of rats on hyper cholesterolemicdiet.” Journal of nutritional science and vitaminology 1984;30.4: 357-372.

[18] Austin MA, Hokanson JE, Brunzell JD. Characterization of low-density lipoprotein subclasses: méthodologie approaches and clinical relevance. Current opinion in lipidology. 1994 1;5(6):395-403.

[19] Krauss RM. Low-density lipoprotein subclasses and risk of coronary artery disease. Current Opinion in Lipidology. 1991 Aug zz1;2(4):248-52.

[20] Strolien, H H, Kriketos, AD, Calvert,GD, Baur,L A and Jenkins . “Fatty Acids, Triglycerides and Syndromes of Insulin Resistance. Prostaglandins and Plasma Lipid and Lipoprotein Metabolism in Human: A Critical Review, Diabetes Care, 2007;30 (4): 1012- 1024.

[21] Singh, Ram B, et al. “Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian experiment of infarct survival-4. Cardiovascular drugs

and therapy1997; 11(3) : 485-491.

[22] Caterina, RD, Madonna, Lotto, and Schmidt, "N-3 Fatty Acids in the Treatment of Diabetic Patients," Diabetes Care.2007; 30 (4): 1012- 1024

[23] Yamashita S, Sakai N, Hirano K, Ishigami M, Maruyama T, Nakajima N, Matsuzawa Y. Roles of plasma lipid transfer proteins in reverse cholesterol transport. Front Biosci. 2001;6:D366-D387

[24] Mack WJ, Krauss RM, Hodis HN. Lipoprotein subclasses in the Monitored Atherosclerosis Regression Study (MARS): treatment effects and relation to coronary angiographic progression. Arterioscler Thromb Vasc Biol. 1996;16:697-704.

[25] Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. JAMA. 1996;276:882-888.

[26] Tornvall P, Bavenholm P, Landou C, de Faire U, Hamsten A. Relation of plasma levels and composition of apolipoprotein B-containing lipoproteins to angiographically defined coronary artery disease in young patients with myocardial infarction. Circulation. 1993;88(5 Pt 1):2180-2189.